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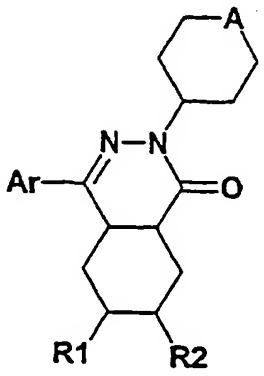
(54) Title: TETRAHYDROTHIOPY RANPHTHALAZINONE DERIVATIVES AS PDE4 INHIBITORS



(I)

(57) Abstract: The compounds of formula (I) in which R1, R2, A and Ar have the meanings as given in the description are novel effective PDE4 inhibitors.

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TETRAHYDROTHIOPY RANPHTHALAZINONE DERIVATIVES AS PDE4 INHIBITORS

Field of application of the invention

The invention relates to novel tetrahydrothiopyran-derivatives, which are used in the pharmaceutical industry for the production of medicaments.

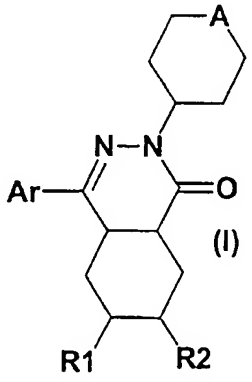
Known technical background

International Patent Applications WO98/31674, WO99/31071, WO99/31090 and WO99/47505 disclose phthalazinone derivatives having selective PDE4 inhibitory properties. In the International Patent Application WO94/12461 and in the European Patent Application EP 0 763 534 3-aryl-pyridazin-6-one and arylalkyl-diazinone derivatives are described as selective PDE4 inhibitors.

Description of the invention

It has now been found that the tetrahydrothiopyran-derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I



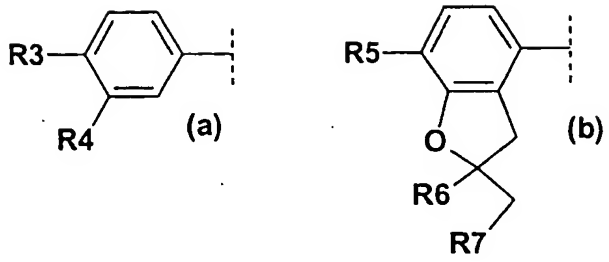
(I)

in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur), S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen, 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is halogen, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

and the salts of these compounds, with the proviso, that those compounds of formula I are excluded, in which A represents S (sulfur) and Ar represents a benzene derivative of formula (a) and both of R3 and R4 are other than halogen.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-8C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Alkoxy radicals having 1 to 8 carbon atoms which may be mentioned in this context are, for example, the octyloxy, heptyloxy, isoheptyloxy (5-methylhexyloxy), hexyloxy, isohexyloxy (4-methylpentyloxy), neohexyloxy (3,3-dimethylbutoxy), pentyloxy, isopentyloxy

(3-methylbutoxy), neopentyloxy (2,2-dimethylpropoxy), butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

Halogen within the meaning of the present invention is bromine, chlorine and fluorine.

3-7C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy and cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

Suitable salts for compounds of the formula I are all acid addition salts. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

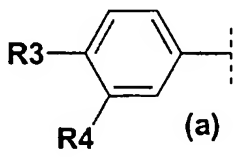
According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

One embodiment (embodiment 1) of the invention are compounds of formula I in which

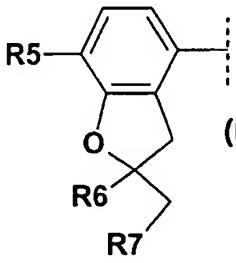
R1 and R2 are both hydrogen or together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



(a)



(b)

wherein

R3 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

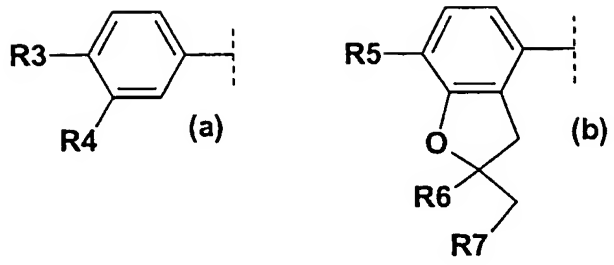
and the salts of these compounds.

Compounds of formula I of embodiment 1 which are to be emphasized are those in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is 1-2C-alkoxy, or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen, 1-4C-alkoxy or 3-5C-cycloalkoxy,

R5 is 1-2C-alkoxy, or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is methyl,

R7 is hydrogen,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

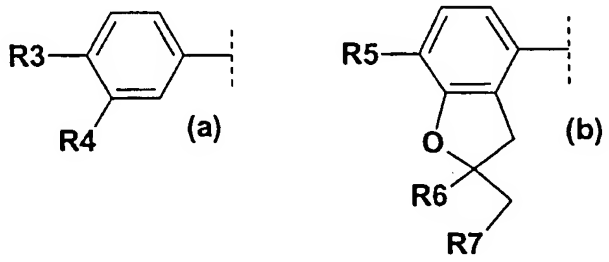
and the salts of these compounds.

Compounds of formula I of embodiment 1 which are particularly to be emphasized are those in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is methoxy or ethoxy,

R4 is chlorine, methoxy, ethoxy or cyclopentyloxy,

R5 is methoxy,

R6 is methyl,

R7 is hydrogen,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

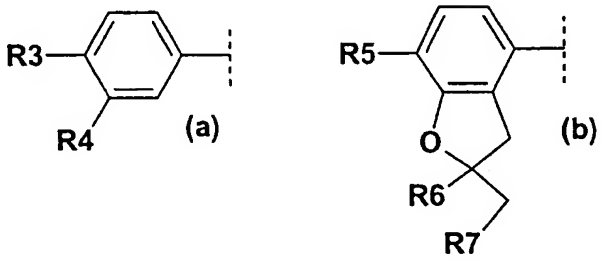
and the salts of these compounds.

A further embodiment (embodiment 2) of the invention are compounds of formula I in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is 1-2C-alkoxy, or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is 1-4C-alkoxy,

R5 is 1-2C-alkoxy, or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is methyl,

R7 is hydrogen,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

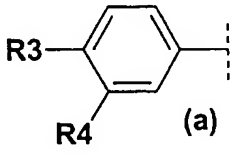
and the salts of these compounds.

Compounds of formula I of embodiment 2 which are to be emphasized are those in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a)



wherein

R3 is methoxy,

R4 is methoxy,

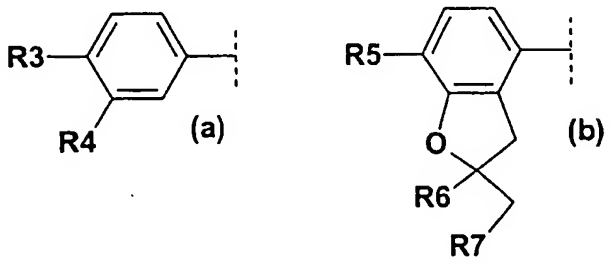
and the salts of these compounds.

A further embodiment (embodiment 3) of the invention are compounds of formula I in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen,

R5 is halogen, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

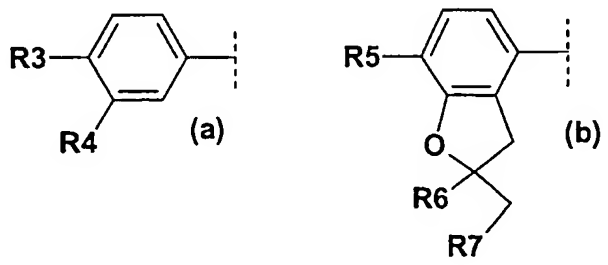
and the salts of these compounds.

Compounds of formula I of embodiment 3 which are to be emphasized are those in which

R1 and R2 together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is chlorine,

R5 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is methyl

R7 is hydrogen,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

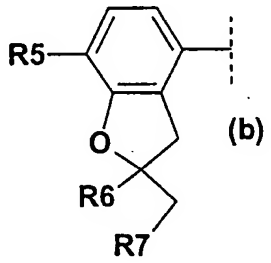
and the salts of these compounds.

A further embodiment (embodiment 4) of the invention are compounds of formula I in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (b)



(b)

wherein

R5 is halogen, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

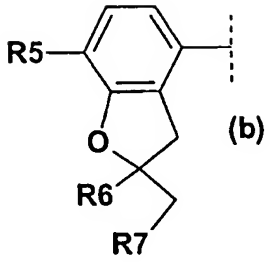
and the salts of these compounds.

Compounds of formula I of embodiment 4 which are to be emphasized are those in which

R1 and R2 together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (b)



wherein

R5 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is methyl

R7 is hydrogen,

or wherein

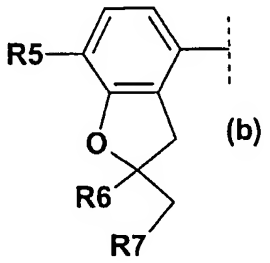
R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

and the salts of these compounds.

Compounds of formula I of embodiment 4 which are particularly to be emphasized are those in which R1 and R2 together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (b)



wherein

R5 is methoxy,

R6 is methyl and

R7 is hydrogen,

and the salts of these compounds.

The compounds of formula I are chiral compounds. Chiral centers exist in the compounds of formula I in the positions 4a and 8a. In case Ar represents a benzene derivative of formula (b) there is one further chiral center in the dihydrofuran-ring, if the substituents -R6 and -CH_2R7 are not identical. However, preferred are in this connection those compounds, in which the substituents -R6 and -CH_2R7 are

identical or together and with inclusion of the two carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring.

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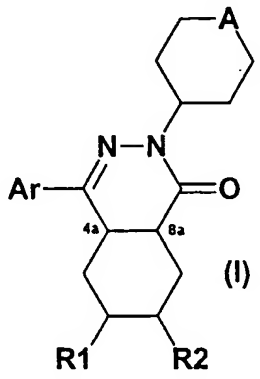
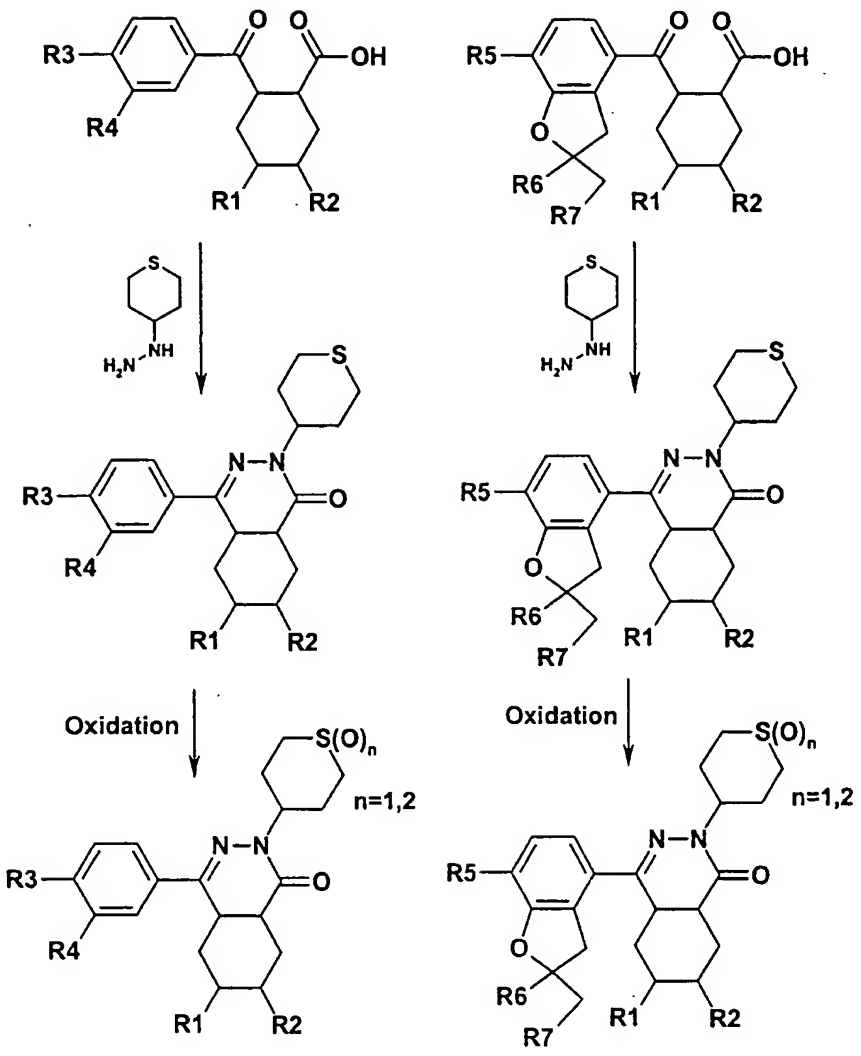


(I)

Therefore the invention includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds, in which the hydrogen atoms in the positions 4a and 8a are cis-configurated. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a. Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers during the preparation with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example, starting compound A1 and A3). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of 1-phenylethylamine [(R)-(+)-1-phenylethylamine = (R)-(+)-α-methylbenzylamine or (S)-(-)-1-phenylethylamine = (S)-(-)-α-methylbenzylamine) and ephedrine, the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

The compounds according to the invention can be prepared, for example, as described in Reaction Scheme 1:



The reaction of the cyclohexanecarboxylic acids or 1,2,3,6-tetrahydrobenzoic acids with 4-hydrazino-tetrahydrothiopyran results in the formation of compounds of formula I. The tetrahydrothiopyran compounds can be converted into sulfones and sulfoxides of formula I through an oxidation reaction.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The preparation of the cyclohexanecarboxylic acids and 1,3,5,6-tetrahydrobenzoic acids is described, for example, in WO98/31674, WO99/31090 and WO99/47505.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the residue obtained from a suitable solvent or

subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula I, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

Examples

Final products

1. **(cis)-4-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-yl)-2-(tetrahydrothiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A solution of 2.0 g of starting compound A1 and 2.0 g of 4-hydrazinotetrahydrothiopyran hydrochloride in 20 ml of pyridine is refluxed for 40 h. After evaporating the reaction mixture, the residue is dissolved in diethyl ether. This solution is washed successively with 1N hydrochloric acid and aqueous sodium carbonate. The ether solution is dried over magnesium sulfate and evaporated. Crystallised from methanol. Yield: 0.8 g. M. p. 163-164°C.

2. **(cis)-4-(3,4-Dimethoxyphenyl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A solution of 0.65 g of 3-chloroperbenzoic acid in 5 ml of dichloromethane is added slowly to a solution of 0.5 g of starting compound A2 in 5 ml of dichloromethane at 0°C. The resulting mixture is stirred for 1 h at 0°C and then1 h at room temperature. Subsequently the mixture is diluted with 100 ml of dichloromethane. This solution is washed successively with a 1 molar solution of sodium thiosulfate and aqueous sodium carbonate, dried over magnesium sulfate and evaporated. The compound is purified by chromatography and crystallised from diethyl ether. Yield: 0.4 g. M. p. 196-198°C.

3. **(cis)-4-(3,4-Dimethoxyphenyl)-2-(1-oxo-hexahydro-1l^4-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from 0.43 g of starting compound A2 and 0.27 g of 3-chloroperbenzoic acid as described for compound 2. Isolated as a mixture of the α and β sulfoxide Yield: 0.2 g. M. p. 158-159°C.

4. **(cis)-4-(3-Chloro-4-methoxyphenyl)-2-(tetrahydrothiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A solution of 10 mmol of (cis)-4-(3-Chloro-4-methoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (prepared as described in WO99/47505) and 15 mmol of 4-hydrazinotetrahydrothiopyran hydrochloride in 20 ml of pyridine are refluxed for 40 h. After evaporating the reaction mixture, the residue is dissolved in diethyl ether. This solution is washed successively with 1N hydrochloric acid and aqueous sodium carbonate.

The ether solution is dried over magnesium sulfate and evaporated. Crystallised from methanol. M. p. 170-171°C.

5. **(cis)-4-(3-Chloro-4-methoxyphenyl)-2-(1-oxo-hexahydro-1l^4-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from 5 mmol of compound 4 and 5 mmol of 3-chloroperbenzoic acid as described for compound 2. Isolated as a mixture of the α and β sulfoxide. M. p. 197-199°C.

6. **(cis)-4-(3,4-Diethoxyphenyl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from starting compound A4 as described for compound 2. M. p. 195-197 °C.

7. **(cis)-4-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-yl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared from compound 1 as described for compound 2. M. p. 261-263°C.

8. **(4aR,8aS)-(cis)-4-(3,4-Dimethoxyphenyl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A solution of 5 mmol of the salt of (R)-(+)-α-methylbenzylamine, (cis)-2-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (prepared as described in WO98/31674) and 7 mmol of 4-hydrazinotetrahydrothiopyrane hydrochloride in 20 ml of pyridine is refluxed for 18 h after which the solvent is evaporated. The residue is dissolved in ethyl acetate and this solution is washed successively with diluted hydrochloric acid and aqueous sodium carbonate. After drying over magnesium sulfate the solvent is evaporated. The residue is treated with 5 mmol of 3-chloroperbenzoic acid as described for compound 2. Crystallised from methanol. M. p. 200-202°C.

9. **(4aS,8aR)-(cis)-4-(3,4-Dimethoxyphenyl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

Prepared as described for compound 8 using (S)-(-)-α-methylbenzylamine instead of (R)-(+)-α-methylbenzylamine. M. p. 203-204°C.

10. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,1-dioxohexahydro-1l^6-thiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from starting compound A5 and 3-chloroperbenzoic acid as described for compound 2. M. p. 214-215°C.

Starting Compounds

A1. (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)-1,2,3,6-tetrahydro-benzoic acid

Prepared as described in WO99/31090.

A2. (cis)-4-(3,4-Dimethoxyphenyl)-2-(tetrahydrothiopyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared as described in WO98/31674.

A3. (cis)-2-(3,4-Diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO99/47505.

A4. (cis)4-(3,4-Diethoxyphenyl)-2-(tetrahydropyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from 10 mmol of starting compound A3 and 15 mmol of 4-hydrazinotetrahydrothiopyrane hydrochloride as described for compound 1. M. p. 127-129°C.

A5. (cis)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(tetrahydropyran-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A solution of 10 mmol of (cis)-4-(3-Cyclopentyloxy-4-methoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid and 15 mmol of 4-hydrazinotetrahydrothiopyran hydrochloride in 20 ml of pyridine are refluxed for 40 h. After evaporating the reaction mixture, the residue is dissolved in diethyl ether. This solution is washed successively with 1N hydrochloric acid and aqueous sodium carbonate. The ether solution is dried over magnesium sulfate and evaporated. Crystallised from methanol. M. p. 116-117°C.

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alz-

heimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to medicaments for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula I according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries, e.g. in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar with auxiliaries which are suitable for the desired pharmaceutical formulations on account of his expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters, can be used.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. To do this, these are either administered directly as a powder (preferably in micronized form) or by atomizing solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarly between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

In the investigation of PDE 4 inhibition on the cellular plane, the activation of inflammatory cells is ascribed particular importance. An example is FMLP (N-formyl-methionyl-leucyl-phenylalanine)-induced superoxide production of neutrophilic granulocytes, which can be measured as luminol-amplified chemiluminescence. (Mc Phail LC, Strum SL, Leone PA and Sozzani S, The neutrophil respiratory burst mechanism. In "Immunology Series" 57: 47-76, 1992; ed. Coffey RG (Marcel Decker, Inc., New York-Basel-Hong Kong)).

Substances which inhibit chemiluminescence and cytokine secretion and the secretion of proinflammatory mediators on inflammatory cells, in particular neutrophilic and eosinophilic granulocytes, T-lymphocytes, monocytes and macrophages are those which inhibit PDE 4. This isoenzyme of the phosphodiesterase families is particularly represented in granulocytes. Its inhibition leads to an increase in the intracellular cyclic AMP concentration and thus to the inhibition of cellular activation. PDE 4 inhibition by the substances according to the invention is thus a central indicator for the suppression of inflammatory processes. (Giembycz MA, Could isoenzyme-selective phosphodiesterase inhibitors render bronchodilatory therapy redundant in the treatment of bronchial asthma?. Biochem Pharmacol 43: 2041-2051, 1992; Torphy TJ et al., Phosphodiesterase inhibitors: new opportunities for treatment of asthma. Thorax 46: 512-523, 1991; Schudt C et al., Zardaverine: a cyclic AMP PDE 3/4 inhibitor. In "New Drugs for Asthma Therapy", 379-402, Birkhäuser Verlag Basel 1991; Schudt C et al., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca; Naunyn-Schmiedebergs Arch Pharmacol 344; 682-690, 1991; Tenor H and Schudt C, Analysis of PDE isoenzyme profiles in cells and tissues by pharmacological methods. In „Phosphodiesterase Inhibitors", 21-40, „The Handbook of Immunopharmacology", Academic Press, 1996; Hatzelmann A et al., Enzymatic and functional aspects of dual-selective PDE3/4-Inhibitors. In „Phosphodiesterase Inhibitors", 147-160, „The Handbook of Immunopharmacology", Academic Press, 1996.

Inhibition of PDE 4 activity

Methodology

The activity test was carried out according to the method of Bauer and Schwabe, which was adapted to microtitre plates (Naunyn-Schmiederberg's Arch. Pharmacol. 311, 193-198, 1980). In this test, the PDE reaction is carried out in the first step. In a second step, the resultant 5'-nucleotide is cleaved to the uncharged nucleoside by a snake venom 5'-nucleotidase from Crotalus Atrox. In the third step, the nucleoside is separated from the remaining charged substrate on ion exchange columns. The columns are eluted directly into minivials using 2 ml of 30 mM ammonium formate (pH 6.0), to which a further 2 ml of scintillation fluid is added for counting.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the examples.

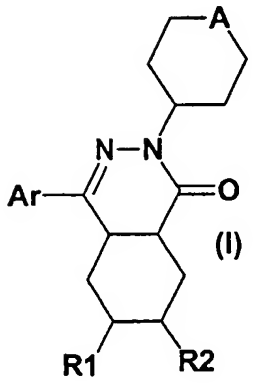
Table A

Inhibition of PDE4 acitivity [measured as -logIC_{50} (mol/l)]

compound	-logIC_{50}
1	9.34
2	8.45
3	8.51
5	8.20
6	8.02
7	9.00
9	9.20
10	9.43

Patent claims

1. Compounds of formula I

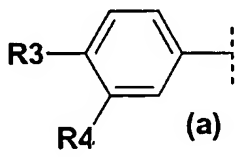


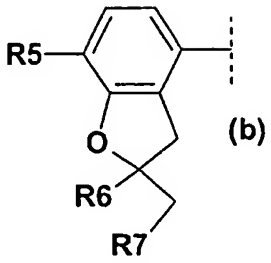
in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur), S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)





wherein

R3 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen, 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is halogen, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

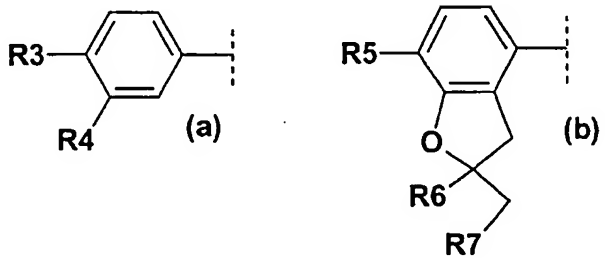
and the salts of these compounds, with the proviso, that those compounds of formula I are excluded, in which A represents S (sulfur) and Ar represents a benzene derivative of formula (a) and both of R3 and R4 are other than halogen.

2. Compounds of formula I according to claim 1 in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is halogen, 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

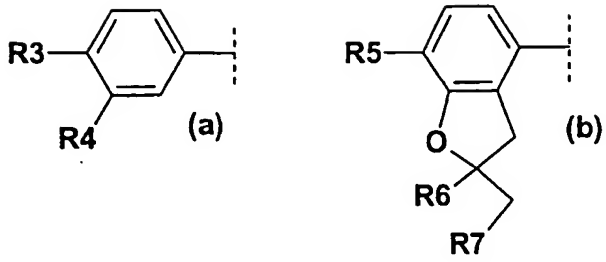
and the salts of these compounds.

3. Compounds of formula I according to claim 1 in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 is methoxy or ethoxy,

R4 is chlorine, methoxy, ethoxy or cyclopentyloxy,

R5 is methoxy,

R6 is methyl,

R7 is hydrogen,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

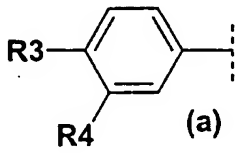
and the salts of these compounds.

4. Compounds of formula I according to claim 1 in which

R1 and R2 together form an additional bond,

A represents S(O) (sulfoxide) or $S(O)_2$ (sulfone),

Ar represents a benzene derivative of formula (a)



wherein

R3 is methoxy,

R4 is methoxy,

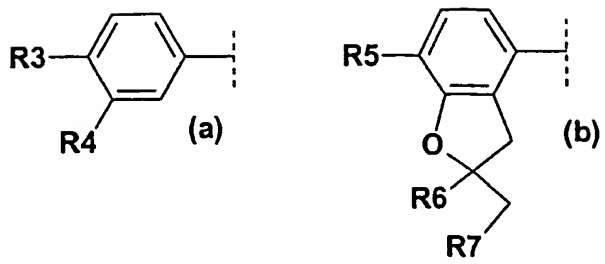
and the salts of these compounds.

5. Compounds of formula I according to claim 1 in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (a) or (b)



wherein

R3 1-4C-alkoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R4 is halogen,

R5 is halogen, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

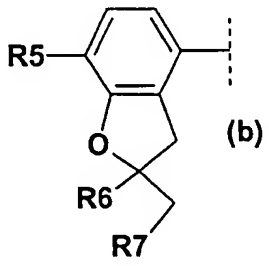
and the salts of these compounds.

6. Compounds of formula I according to claim 1 in which

R1 and R2 are both hydrogen or together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (b)



wherein

R5 is halogen, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkyl and

R7 is hydrogen or 1-4C-alkyl,

or wherein

R6 and R7 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

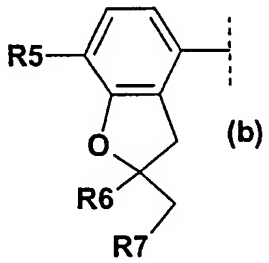
and the salts of these compounds.

7. Compounds of formula I according to claim 1 in which

R1 and R2 together form an additional bond,

A represents S (sulfur),

Ar represents a benzene derivative of formula (b)



(b)

wherein

R5 is methoxy,

R6 is methyl and

R7 is hydrogen,

and the salts of these compounds.

8. Compounds of formula I according to one of the claims 1, 2, 3, 4, 5, 6 or 7 in which the hydrogen atoms in the positions 4a and 8a are cis-configurated.

9. Compounds of formula I according to one of the claims 1, 2, 3, 4, 5, 6 or 7 in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

10. Medicaments containing one or more compounds of formula I according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 00/10445

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/04 C07D409/14 A61K31/502 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 31674 A (BYK GULDEN LOMBERG CHEM FAB ;STERK GEERT JAN (NL)) 23 July 1998 (1998-07-23) cited in the application page 40, compound 125 claims 1,8-10	1-10
Y	WO 99 31071 A (BYK GULDEN LOMBERG CHEM FAB ;STERK GEERT JAN (NL)) 24 June 1999 (1999-06-24) cited in the application claims 1,8-10	1-10
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEM FAB ;ULRICH WOLF RUEDIGER (DE); STERK GEER) 24 June 1999 (1999-06-24) cited in the application claims 1,7-9	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2001	23/02/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte :onal Application No
PCT/EP 00/10445

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9831674 A	23-07-1998	AU 5862998 A	07-08-1998
		BR 9806752 A	14-03-2000
		CN 1249749 T	05-04-2000
		EP 0971901 A	19-01-2000
		NO 993301 A	10-09-1999
		PL 334561 A	13-03-2000
		SK 95199 A	10-12-1999
		US 6103718 A	15-08-2000
WO 9931071 A	24-06-1999	AU 1760399 A	05-07-1999
WO 9931090 A	24-06-1999	AU 2270199 A	05-07-1999
		EP 1042319 A	11-10-2000